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CANCER PAIN (D MARCUS, SECTION EDITOR)

Managing Difficult Pain Conditions in the Cancer Patient

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Abstract Whereas most pain due to cancer can be relieved with relatively simple methods using oral analgesics, as suggested by WHO guidelines, some patients may have difficult pain situations that require more complex approaches. It is estimated that 10–20 % of cancer patients suffer from pain that is not easily relieved. There are a number of factors that may reduce the efficacy of opioids in the management of cancer pain. Neuropathic pain (NP) and breakthrough pain (BP), especially of the incident subtype, have been identified as challenges for clinicians. In several prognostic studies, these two mechanisms were associated with limited positive outcomes compared with other syndromes. Opioid-induced hyperalgesia has recently been described as representing a challenge for physicians in the clinical setting. The global response to opioids, including the development of adverse effects, typically varies by individual and is likely genetically determined. Moreover, clinical evidence suggests that different opioids may produce different effect profiles, and so it is more appropriate to consider the response to each individual opioid rather than general opioid response. This paper will review both pharmacological and procedural mechanisms and treatments of these difficult pain syndromes.

Keywords Cancer pain · Neuropathic pain · Opioid-induced hyperalgesia · Breakthrough pain · Incident pain

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Introduction

The prevalence of cancer pain ranges from 25 % to 75 %, depending upon the stage of disease. Pain prevalence is even higher in developing countries due to greater incidence of late-stage diagnosis [1]. Chronic opioid therapy is generally recognized as standard management for cancer pain. Analgesia can be achieved with opioid dosage that varies by patient, as there is effectively no ceiling to the analgesic effect, and the proportion of adverse effects that the patient can tolerate is usually the limiting factor of the dose used. Whereas most pain due to cancer can be relieved with relatively simple methods using oral analgesics, WHO guidelines suggest that 10–20 % of cancer patients have pain that is not easily relieved and that requires a more complex approach [2].

The results of several studies on factors and pain prognosis indicate that younger age, neuropathic pain, incident pain, psychological distress, and baseline pain intensity have been found to be associated with more difficult pain control [3]. Breakthrough pain and psychological distress have been confirmed as key variables of a future classification system. Candidate variables include sleep, opioid dose, pain mechanism, use of non-opioids, pain localization, cancer diagnosis, location of metastases, and addiction [4].

As opioids are the most commonly used drugs, and as patients with difficult pain syndromes are assumed to use this class of drug, the principal focus of research has been opioid responsiveness and the factors influencing it. There is an immense variability in responsiveness across patients and in responses over time. This broad range extends from patients who easily achieve analgesia that is maintained with few dosage adjustments to those who are completely unresponsive and experience no pain relief at doses associated with intractable adverse effects [5].

The need for opioid escalation may indicate an abrupt change in the underlying disease or the presence of a previously unknown complication affecting the dose/response relationship. There is a series of factors that may play a role,

including any process that reduces the efficacy of the current analgesic approach, the occurrence of tolerance, the appearance of intractable adverse effects and symptoms other than pain, type and temporal pattern of pain, morphine/metabolite ratio, individual factors, and primary psychological processes. The presence of very advanced disease and associated multiorgan failure may further confound the clinical picture.

Neuropathic pain (NP) and breakthrough pain (BP), especially of the incident subtype, have been identified as challenging situations for clinicians. In several prognostic studies, these two mechanisms were found to be associated with limited chance of positive outcome as compared with other syndromes. Another recent challenge for physicians is opioid-induced hyperalgesia associated with unsuccessful dose escalation. This review will focus on mechanisms and treatments of these difficult pain syndromes.

Neuropathic Pain

NP occurs most commonly as a consequence of tumor compression or infiltration of peripheral nerves or the spinal cord. Trauma and chemical- or radiation-induced injury as a result of surgery, chemotherapy, or radiotherapy may also result in this type of pain. NP syndromes are a major issue in the treatment of cancer pain [6]. Difficulties in elucidating underlying mechanisms of NP have been reported [7], and no universally accepted and validated clinical diagnostic criteria exist for NP.

NP is not a single entity, but a heterogeneous group of conditions that differ in etiology and location, and in which classification of the pain has been limited to either underlying cause or anatomical site [8•]. Recent scientific debate has arisen around the question of whether NP could be better categorized according to a hierarchical classification as definite, possible, and unlikely [9••]. Cancer pain is an even more complex and dynamic issue, and while a considerable neuropathic component is often present, the pain mechanism is mixed and may involve multiple concomitant variables.

The opioid response in cancer NP has been a controversial topic in the last decades. NP has been described as a possible negative predictive/prognostic factor in cancer pain therapy associated with a relative decreased responsiveness to systemic opioids. The NP mechanism does not result in an inherent resistance to opioids but may decrease the likelihood of a favorable outcome [5, 10]. Further prognostic studies have shown that NP is associated with more complex treatments, requiring more adjuvants and higher final opioid doses [3].

Clinical observation suggests that change in opioid responsiveness is dependent on the context and likely the specific type of nerve injury. In a recent survey, opioids were clinically effective in "definite NP" conditions, although more aggressive treatment requiring careful utilization of opioids and symptomatic drugs was necessary. The presence of NP may also influence the opioid response in some ways, as patients with definite NP are more likely to require complex treatment involving symptomatic drugs and/or opioid switching [11•]. Although patients with NP may be more likely to require higher doses of opioids to achieve acceptable analgesia (which is often accompanied by greater toxicity), the NP mechanism does not result in an inherent resistance to opioids [3, 11•]. Moreover, the response attained with one drug cannot be generalized to other opioids. This is consistent with the successful use of an alternative opioid in cancer patients who are refractory to previous opioids [11•].

Drugs Used for NP in Cancer Patients

One alternative for the NP patient who is poorly responsive to opioids is the co-administration of a non-opioid analgesic. A recent review based on existing evidence suggests that opioids alone can be effective in NP and that, with skillful prescribing, the addition of antiepileptic or antidepressant adjuvants may improve pain outcomes. Evidence indicates that the best outcome would be achieved with gabapentin, although the expected benefit is a one-point reduction in ADP score for approximately one week, which is less than that reported in non-cancer population (NTT differs from NNH). A combination of lower opioid doses and adjuvants may result in a better outcome [12].

Evidence for other drugs such as sodium channel-blocking agents (e.g., systemic local anesthetics) is even less consistent. Corticosteroids may have a general positive effect on various cancer-related symptoms, including pain, appetite, energy level, food consumption, and general well-being. Although there are reports of analgesia in diverse pain syndromes, most of this evidence is anecdotal.

Agents that block activity of NMDA receptors may provide new tools for the treatment of poorly responsive pain syndromes, and particularly neuropathic pain. Ketamine is a noncompetitive NMDA receptor blocker that exerts its primary effect when the NMDA-receptor-controlled ion channel has been opened by a nociceptive barrage. A synergistic effect between ketamine and opioids has been observed in cancer patients with NP who have lost an analgesic response to high doses of morphine. In controlled studies, ketamine was effective in reducing pain intensity in patients receiving opioids for cancer-related NP [13].

A recent large randomized controlled trial concluded that ketamine does not have a clinical benefit when added to opioid in cancer patients with a refractory pain condition [14]. However, the profiles of study participants suggest that they were not ideal candidates for ketamine treatment. Anecdotal experience indicates that less than 50 % of patients are responsive to ketamine, and therefore any controlled study will be inferred by the number of patients who are non-responders. For example, enrichment studies could provide

different results, particularly in a select population of patients with complex pain situations. Randomized controlled studies are challenging in advanced cancer patients. However, strict protocols often do not reflect daily practice, where flexibility according to clinical situation is the guide to providing the best solution for individual patients. Existing evidence is inadequate to resolve certain extreme and complex pain situations. In situations where standard analgesic options have failed, ketamine may be a reasonable option [15].

Ketamine should be given at an initial dose of 100–150 mg daily, and opioid dose should be reduced by 50 %, with dose titrated against the effect. Responders should be selected with appropriate test dosing. Unfortunately, use of this drug is associated with certain central psychomimetic reactions that warrant expertise and caution in treatment. In certain cases, after systemic analgesics and multiple opioid trials have failed, spinal analgesia with a combination of local anesthetics and opioids may be helpful.

Opioid-Induced Hyperalgesia (OIH)

Clinical reports suggest that opioids, which are intended to eliminate pain, can unexpectedly produce abnormally heightened pain sensations characterized by a lowering of the pain threshold, commonly known as opioid-induced hyperalgesia (OIH) [16]. Such abnormal sensations have been described as being quantitatively different from normal pain sensation and differentially localized from the site of the original pain, which could result in an exacerbation rather than an attenuation of excitatory behaviors.

The precise molecular mechanism as described in the basic science literature varies substantially. It is generally thought to result from neuroplastic changes in the nervous system, leading to sensitization of pronociceptive pathways. The causative mechanisms of of OIH have been attributed to the central glutaminergic system, spinal dynorphins, and descending facilitation, which may all play a relevant role in producing a pronociceptive state [17].

Although much experimental data exist to explain these clinical changes of opioid response, no data exist on how, when, and why this occurs, or if it is a simple consequence of a rapid derangement of the central nervous system, possibly occurring in the last days of life. Clinicians should suspect OIH when the effect of opioid treatment appears to wane in the absence of disease progression in the context of unexplained pain reports or diffuse allodynia not associated with the original pain, as well as increased levels of pain with increasing dosages [18].

OIH Treatment Strategies

In the case of rapid opioid dose escalation, development of hyperalgesia should be suspected, and alternative procedures should be considered to break this vicious circle before pain conditions worsen irreversibly. The presumed offending drug should be stopped, and a rapid opioid substitution should be started. Opioid switching in this context is problematic, given that dose calculation is often an issue, particularly when switching to methadone. Thus, starting doses should be lower than would otherwise be expected. Individualization of treatment and strict surveillance are essential [19•].

Despite several reports that this strategy may be helpful, evidence is still weak, given the poor design and small sample size typical of these studies. The treatment includes rational polypharmacy with non-opioid medications. Adjuvant drugs may be useful in reducing the need for opioid escalation and minimizing the opioid dosage. Finally, the use of NMDA receptor antagonists such as ketamine may be helpful, although data are sparse and anecdotal [16]. As mentioned above, use of this drug requires a high level of experience.

Interventional pain management – for example, spinal analgesia – can reduce the need for pharmacotherapy altogether. Interventional procedures may be helpful when the previous strategies have been exhausted (see below).

Breakthrough Pain – Pain on Movement

Breakthrough pain (BP) has recently been defined as a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger despite relatively stable and adequately controlled background pain [20]. In various surveys, 64–90 % of cancer patients with pain have been reported to experience these intermittent flares of pain [21], although these figures may be biased due to selection of patients referred to large cancer hospitals for complex pain situations.

Although BP is related to a large variety of etiologies and different pain mechanisms, many such events are caused by the presence of bone metastases. This condition is frequently – although not absolutely – a predictable condition, and patients learn to limit certain movements to avoid increased pain, which may also be absent at rest or controlled by analgesic drugs. As a consequence, BP strongly interferes with most daily activities, adversely affecting quality of life. The transitory exacerbation of pain that occurs on a background of a stable pain in patients receiving chronic opioid therapy – due primarily to movement in patients with bone metastases – is very difficult to treat because the opioid dose required to control the episode may produce unacceptable side effects when the patient is at rest. Some patients must remain immobile or refrain from performing pain-causing movements.

General Treatment of BP, Incident Type

Of paramount importance in the treatment of BP is attention to precipitating or alleviating factors that help prevent or reduce

the occurrence of pain exacerbation. Radiotherapy, radionuclides, and bisphosphonates have been reported to reduce pain and the occurrence of fracture, as well as the development of new osteolytic lesions, resulting in an improvement in quality of life. However, only recently has there been consideration given to the need to measure the analgesic effects of such treatments [22]. Rehabilitation approaches may also be helpful. Protection with orthotic devices may be useful for upper-extremity bone lesions. The lower extremities are not amenable to this method, however, because of the high degree of load. As a result, bone involvement of the lower extremities often results in loss of mobility. Impeding fractures require surgical stabilization using fixation devices or prosthetic reconstruction. Surgical stabilization of the vertebral column and extremities may dramatically improve the quality of life, decrease incident pain, and prevent complications associated with immobility. In advanced cancer patients with poor performance status, risks vs. benefits should be weighed with regard to such interventions.

Pharmacologic Treatment of BP

Basal opioid medication, which is otherwise considered acceptable, is often given to patients with movement-related pain due to bone metastases. These patients have limited mobility and are usually confined to bed. NSAIDs may be useful in improving basal analgesia, and although the specific efficacy of NSAIDs in bony pain has not been appropriately assessed, an occasional relevant response can be observed individually in patients.

One important consideration is the optimization of basal analgesia by an appropriate opioid titration to obtain the best balance between analgesia and adverse effects, as well as using different sequences of opioids and combining analgesics and adjuvants when necessary. There are several reasons to optimize the basal analgesia with opioid and non-opioid drugs, particularly in the presence of frequent and intense episodes of BP. In some cases, no medication has an onset so rapid as to parallel an acute temporal pattern of pain firing. The development of pain may be too fast after initiating a volitional movement such as walking, cough, sitting, or standing, or an involuntary movement in bed. If medications are given for incident pain, the pain may spontaneously subside before the drug shows a significant effect. On the other hand, incident pain may be an expression of poor basal pain relief or apparent analgesia. A study of patients presenting a relevant incident component showed that most of them responded to further opioid dose increases despite having their pain at rest ostensibly controlled [23]. It is likely that hypersensitivity to some innocuous stimuli such as movement requires higher preemptive doses of basal opioid medication to reduce the increased pain input, and that the opioid dose capable of maintaining good analgesia while resting is insufficient during incident pain.

Patients with pain from bone metastases on weight-bearing or movement, however, may require an opioid dose that causes excessive adverse effects for the patient at rest, as movement-related pain is likely to be repetitive and, in some cases, unpredictable. Once optimization of background analgesia is reached, pain flares can still occur, and are more or less expected, and a pain strategy should be developed to relieve pain in these circumstances. For example, a predictable increase in pain intensity could be relieved for some hours by administering a preemptive dose of oral morphine 30–45 minutes before initiating activity.

The treatment of sudden episodes of incident BP is challenging because it is dependent upon the balance between the level of activity, the need to stop the movement, the spontaneous reduction of pain, and the effect of drugs. The onset of incident pain is very rapid. As pain relief is usually urgently required, modes of administration designed for rapid drug delivery are often preferred. Fentanyl is a potent and strongly lipophilic drug that favors its passage through the mucosa and then across the blood–brain barrier to provide fast analgesia. Different technologies have been developed to provide fast pain relief with fentanyl delivered by non-invasive routes through the buccal and nasal mucosae. All studies performed with rapid-onset opioids (ROOs) have recommended that these drugs be administered to opioid-tolerant patients receiving doses of oral morphine equivalents of at least 60 mg. All of these delivery systems provide fast analgesia within 5–15 minutes [24•].

The choice and dosage of ROO remains controversial. All of the controlled studies have recommended titrating opioid doses for BP. It is not clear why titration is necessary, as the presence of tolerance should suggest a dose proportional to that used for background analgesia. Moreover, dose titration may make the practical use of ROOs difficult in daily activity, particularly at home or in outpatients. Further, specifically designed studies are needed to provide definitive indications on dosing ROOs for BP and which ROO may be preferable in specific scenarios [25].

Interventional Procedures for Difficult Pain Syndromes

Neuraxial techniques are largely used in cancer patients poorly responsive to systemic treatments, including NP, poor opioid response, and the presence of incident pain. With spinal opioids, the degree of analgesia obtained in the treatment of cancer pain is largely variable. These patients commonly have unsuccessfully received several trials of systemic opioids, possibly achieving high doses. The previous aggressive treatment with systemic opioids would leave failed patients unresponsive to opioids, even with intrathecal administration [26]. Morphine remains the opioid of choice because of its convenient systemic/intrathecal potency ratio compared with other

opioids. Intrathecal opioids may offer several advantages over epidural opioids in long-term treatment, including more satisfactory pain relief with lower doses of morphine and fewer technical problems. Because of lower daily doses and volumes, intrathecal treatment has proven to be more suitable for treatment at home by continuous infusion rather than epidural treatment . Volumes are even more important when considering the need to add local anesthetics, as spinal opioids alone do not always provide adequate pain relief in the setting of difficult pain syndromes, and the high doses that are often necessary cause specific or systemic side effects.

Local anesthetics are particularly advantageous in alleviating pain on movement. The morphine/bupivacaine intrathecal treatment has been proven highly effective as demonstrated by the significant pain relief, non-opioid analgesic and sedative consumption, and improved sleep, although walking and gait pattern was not significantly improved due to the location and progression of the illness and motor blockade. Personalization of the mixture is essential to obtain the best balance between analgesic benefit and adverse effects, and requires a high level of expertise. The most frequent indication for spinal treatment is incident pain [27].

Minimally Invasive Procedures

Some invasive approaches have been used extensively in palliative care, although few of these procedures have undergone controlled clinical studies. Percutaneous cervical cordotomy by radiofrequency has been utilized in patients with unilateral bone pain. It usually produces good relief for unilateral, well-localized pain of any origin with the exception of certain neuropathic pain. However, the analgesic effects tend to fade after the procedure, and some pain may persist or develop below or above the level of analgesia. The procedure also carries the risk of worsening pain at other sites (including mirror pain), general fatigue or hemiparesis, and respiratory failure. The high rate of morbidity and mortality suggests strict selection of cases [28].

Invasive procedures are options for the treatment of skeletal metastases in patients who are poor surgical candidates because of their age, comorbidities, or the extent of disease, or who are refractory to radiation therapy [29]. Vertebroplasty is a procedure whereby painful vertebral compression fractures are stabilized by the injection of bone cement. Kyphoplasty differs in that the injection of cement is preceded by the attempted restoration of vertebral height by the inflation of a percutaneously placed intravertebral balloon. These techniques are indicated in an acute painful vertebral body pathologic fracture without the involvement of the spinal canal and its elements [30, 31]. Radiofrequency ablation can provide effective palliation of painful bone metastases. The aim of this procedure is to ablate tumors as widely as possible within the outer margin of the tumor. The mechanism by which radiofrequency ablation provides pain relief is multifold, including the destruction of local sensory nerves, decrease of tumor burden, and prevention of tumor progression. Like

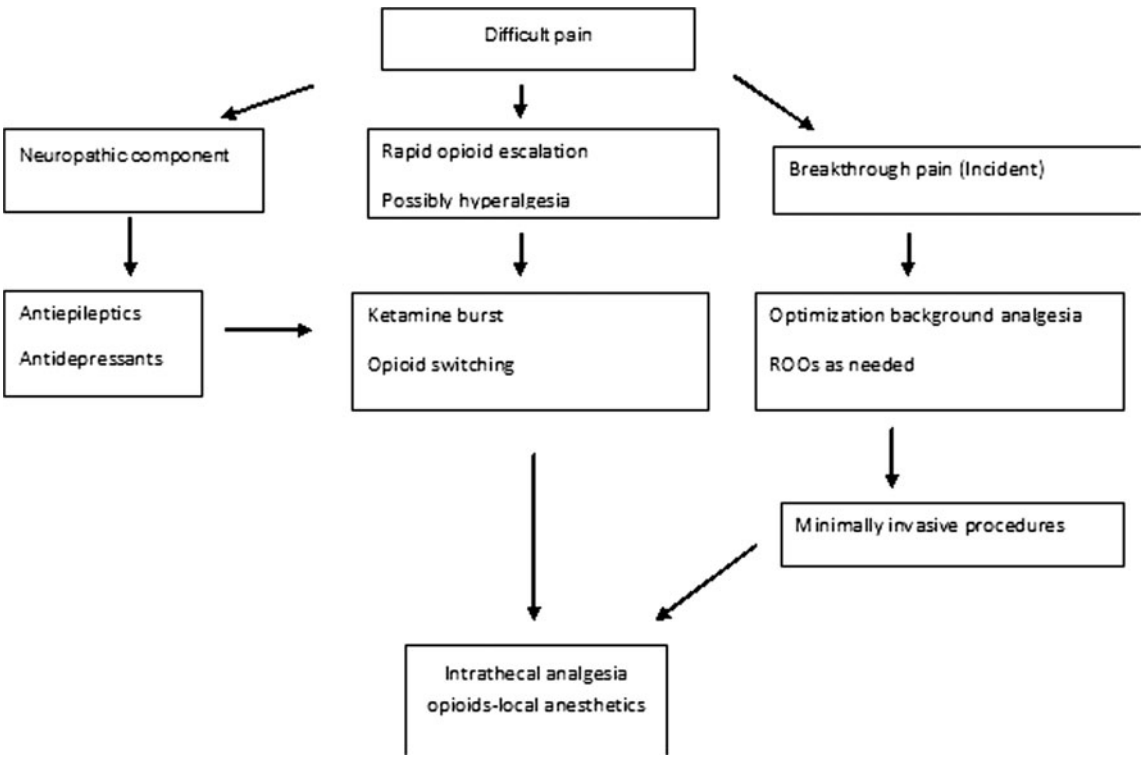

Fig. 1 Flow chart of possible interventions for difficult pain in cancer patients

radiofrequency ablation, percutaneous cryoplasty may provide pain relief through cooling produced by expansion of argon forced into the lesion, generating an ice ball. Cellular dehydration and cell death are the primary mechanisms. All of these techniques may have rare but serious neurological complications.

The exact role of these procedures in the context of cancer disease remains to be determined. The use of these techniques is dependent upon the availability of experts, and requires multidisciplinary evaluation and treatment, rather than a mere technical intervention, to clarify the appropriate patient selection and aims of the procedure in a broad context.

Conclusion

In the context of cancer pain management, there are heterogeneous difficult pain conditions that require careful assessment and more complex strategies. In these circumstances, there is the need for skilled personnel with high levels of experience in the pharmacological treatment of cancer pain, particularly with opioid switching, who are able to individualize the treatment according to the patient's analgesic response. An attempt to provide a general flow chart of decision-making for the conditions examined in this review is shown in Fig. 1. Pain relief is achieved in most cases with pharmacological intervention. However, carefully selected patients unresponsive to systemic analgesia may achieve analgesia with interventional procedures.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Sebastiano Mercadante declares no potential conflicts of interest relevant to this article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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